

## REMARKS

Claims 29, 31-37, 39-45, and 47-55 are pending. All of these claims were rejected under 35 U.S.C. § 112, first paragraph. Claims 34-37, 39-44, and 50-52 were further rejected under 35 U.S.C. § 112, second paragraph. Each of these rejections is addressed below.

### Support for the Amendments

Support for the amendments is found throughout the specification and claims as originally filed. For example, support for the amendment of claims 29 and 45, which now recite neuroleptic therapy, is found at page 79, lines 7-10. Support for the amendment of claims 32, 34, 48, 50, 53, and for new claims 56-62, which recite a mutation that results in decreased MTHFR activity or thermal stability is found, for example, at page 79, lines 11-15. Support for new claims 56-62 is also found at original claims 45-53. Support for new claims 56, 57, and 58, which recite folic acid therapy, is found, for example, at page 55, lines 12-16.

For the record, Applicant does not agree with the present rejections and reserves the right to pursue all canceled subject matter in this, or future, related applications.

### Rejections under 35 U.S.C. § 112, first paragraph

Claims 29, 31-37, 39-45, and 47-55, which feature methods of schizophrenia therapy selection and methods of preventing, treating, or delaying schizophrenia, are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement, on the grounds that the claims are not commensurate in scope with the disclosure. Specifically, the Office asserts that Applicant has failed to enable a method of selecting a therapy for schizophrenia by detecting any MTHFR mutation other than a homozygous MTHFR C677T mutation, have failed to enable methods for selecting a therapy that could delay or prevent the onset of schizophrenia in a subject having any MTHFR mutation, and have failed to enable a method for determining the safety or toxicity of a therapy for schizophrenia in a subject having any MTHFR mutation. Each of the rejections is addressed below.

#### *MTHFR mutations*

The Office first asserts that the specification fails to provide guidance regarding how any MTHFR mutation other than MTHFR C677T is associated with schizophrenia or with therapy selection. The Office states:

The specification teaches “disease causing” mutations in the MTHFR gene can be identified by detecting those mutations which result in decreased activity of the encoded MTHFR protein. The specification does not teach any other types of mutations which are “indicative of MTHFR deficiency”. . . In, fact, the teachings of the specification suggest that benign polymorphisms are not associated with disease . . .

As applied to the present claims, this basis for the rejection may be withdrawn. Applicant's claims are now limited to those MTHFR mutations that decrease enzyme activity or reduce thermal stability. Applicant discloses that such mutations are associated with schizophrenia and an improved response to neuroleptic therapy. For example, at page 79, lines 11-15, Applicant states:

Because the C677T mutation results in decreased MTHFR activity and increased enzyme thermolability, *other MTHFR genotypes or haplotypes having similar characteristics may be associated with schizophrenia or improved response to neuroleptics.*

Thus, Applicant plainly discloses that other MTHFR mutations that are biochemically similar to MTHFR C677T are also associated with schizophrenia.

In addition, the Office asserts that "There is no information provided in the specification to establish that individuals heterozygous for the 677 mutation are more likely to respond to neuroleptic treatment." Contrary to this assertion, Applicant discloses that a statistical analysis of patients grouped by MTHFR genotype identified a significant association between the presence of at least one MTHFR C677T mutation and the responsiveness to neuroleptic therapy (Table 9). With respect to these results, Applicant states:

[T]he most striking finding was observed when patients were stratified according to their quality of response to conventional neuroleptics and long-term outcome. The group of R patients showed a highly significant increase in the frequency of allele V ( $\chi^2=16.77$ ,  $df = 1$ ,  $p= 0.00004$ ) in contrast to the group of NR patients ( $\chi^2 = 0.053$ ,  $df = 1$ ,  $p = 0.81$ ).

Based on these results, Applicant concludes that patients having a heterozygous MTHFR mutation that affects enzyme activity are more likely to respond to neuroleptic therapy.

Applicant states:

We have discovered that the heterozygous form of the C677T mutation in methylenetetrahydrofolate reductase (MTHFR) is more common in patients diagnosed with schizophrenia than in a healthy control population and thus is a risk factor for this disease. In addition, *both the heterozygous and homozygous forms of this mutation are associated with an improved response to neuroleptic treatment* ... (page 79, lines 3-10.)

In addition, the Office questions how the presence of two or more MTHFR mutations affects the selection of a therapy. As indicated in Applicant's specification at page 79, lines 15-25, there is a dosage effect with respect to the presence of multiple mutations and the severity of illness. For example, Applicant discloses that heterozygotes for the C677T mutation have approximately 70% of control MTHFR activity, while double heterozygotes, having the MTHFR C677T mutation and the A1298C mutation, have an additional loss of activity (page 63). Specifically, mothers who are heterozygous for the two mutations have just 62% of control MTHFR activity, and children that are heterozygous for both mutations have just 50% of control MTHFR activity (page 63). As the level of MTHFR activity is reduced in a patient, the patient's homocysteine level typically rises (page 65, lines 12-17), and this increase in homocysteine can cause a worsening of psychotic symptoms (page 83, lines 16-18). Given the increased pathology present in patients having two or more MTHFR mutations that decrease enzyme activity or thermal stability, it follows that these patients are particularly good candidates for

neuroleptic treatment. Because applicant has shown that the presence of two or more MTHFR mutations in a patient influences the selection of a patient therapy, this basis for the rejection should be withdrawn.

In addition, the Office asserts that it is difficult to establish a correlation between an MTHFR allele and the development of a disease, given the unpredictability present in the art. In support of this assertion, the Office cites publications by Zuliani (Acta Neurol Scand 103:304-308, 2001, hereafter “Zuliani”), Gussekloo et al. (J. of Neurology, Neurosurgery, and Psychiatry 67:535-538, 1999, hereafter “Gussekloo”) and Chapman (Stroke, 29:1401-1404, 1998). The Office characterizes Zuliani as failing to describe an association between the C677T mutation and Alzheimer’s disease, cognitive impairment, or vascular dementia. The Office states that Gussekloo fails to describe a correlation between the presence of an MTHFR C677T mutation and dementia in patients over eighty-five years of age, and that Chapman fails to see an association between the presence of an MTHFR C677T mutation and vascular dementia or Alzheimer’s disease.

Given that none of these references addresses the role of MTHFR in schizophrenia, none of the cited references is relevant to Applicant’s current claims, which are limited to methods of *schizophrenia* therapy selection or treatment. This basis for the enablement rejection should be withdrawn.

### *Methods of preventing or delaying schizophrenia*

The second general basis for the enablement rejection focuses on the Office's assertion that Applicant has failed to establish that any therapy could be used to *delay or prevent* the onset of schizophrenia, as recited in claims 45, 48-53, and 55, although the Office acknowledges that Applicant discloses that individuals homozygous for the C677T mutation may benefit from folic acid treatment. Applicant notes that claims 45, 48-53, and 55 are now directed solely to methods of *treating* schizophrenia. Accordingly, the rejection is addressed with respect to new claims 56-62, which are directed to methods of preventing or delaying schizophrenia in a subject by administering folic acid therapy.

In support of these claims, Applicant provides the accompanying Declaration of Dr. Rima Rozen. This Declaration states that diseases (e.g., schizophrenia, premature vascular disease, and arterial and venous thrombotic phenomena) associated with an MTHFR mutation that reduces MTHFR enzyme activity or thermostability share a common defect in folate metabolism that increases plasma levels of homocysteine and contributes to disease pathology. As disclosed in the present specification, Applicant has found that schizophrenia is correlated with an MTHFR C677T mutation, and that patients having this mutation typically have increased levels of homocysteine. Given these facts, it is reasonable to expect that methods that normalize levels of homocysteine, such as increasing plasma folate levels, would prevent or delay a schizophrenia associated with an MTHFR C677T mutation. (Declaration of Dr. Rima Rozen, paragraph 3.)

Moreover, Applicant in the specification discloses that diseases associated with increased homocysteine levels could be prevented, delayed, or treated by increasing plasma folate levels. At page 58, lines 11-19, Applicant states:

Table 4 provides preliminary data for therapeutic intervention by folic acid supplementation to individuals who are homozygous for the alanine to valine change. The data suggest that *higher levels of plasma folate would lead to normalization of homocysteine levels in mutant individuals and might prevent the occurrence of disorders associated with high homocysteine levels . . .*

While the Office asserts that this therapy is only beneficial to patients homozygous for an MTHFR mutation, as evidenced in the Declaration of Dr. Rima Rozen, one skilled in the art understands that increasing folic acid levels prevents or delays diseases associated with high levels of homocysteine in individuals having any type of MTHFR mutation that reduces enzyme activity or thermostability (Declaration of Dr. Rima Rozen, paragraph 4).

As further evidence that diseases associated with an MTHFR mutation can be prevented or delayed with therapy to decrease plasma homocysteine levels, Applicant submits Exhibits A (Christensen et al., *Arterioscler. Thromb. Vasc. Biol.* 17:569-573, 1997, hereafter “Christensen”) and B (Jacques et al., *Circulation* 93:7-9, 1996, hereafter “Jacques”).

Christensen describes a correlation between an MTHFR defect and increased levels of plasma homocysteine in patients with premature coronary artery disease, particularly in patients with low plasma folate levels. Christensen suggests that patients having a genetic predisposition to hyperhomocysteinemia be treated with folate

supplementation to lower plasma homocysteine levels (page 572, left column, first paragraph).

The other reference, Jacques, describes a correlation between the presence of an MTHFR defect and increased levels of plasma homocysteine in patients having low levels of plasma folate. In one exemplary passage, Jacques suggests that hyperhomocysteinemia levels can be prevented by folic acid supplementation. Jacques states:

In conclusion, these findings indicate that individuals with thermolabile MTHFR may have a higher folate requirement for regulation of plasma homocysteine concentrations and, more importantly, *suggest a therapeutic strategy (i.e., folate supplementation) to prevent fasting hyperhomocysteinemia* in such persons. (page 9, left column, first paragraph.)

Applicant's specification discloses that an increased risk of schizophrenia is associated with a genetic mutation in MTHFR that decreases MTHFR activity or thermostability and thereby results in increased plasma levels of homocysteine. Given that a therapy that increases plasma folate levels will prevent or delay hyperhomocysteinemia, it follows that such a therapy would also prevent or delay schizophrenia. This second basis for the enablement rejection may also be withdrawn.

#### *Drug Responsiveness*

With respect to the third basis for the enablement rejection, drug responsiveness, the Office asserts (i) that Applicant has failed to disclose any MTHFR allele that is

associated with the toxicity or safety of a schizophrenia therapy; and (ii) that it is unpredictable how any MTHFR genetic mutation will affect drug responsiveness.

With respect to the first ground for rejection, Applicant notes that claims 29 and 45, and their dependent claims, which are now limited to *treatment* methods and therapy selection methods featuring an efficacious neuroleptic therapy, no longer recite the term “safe.” This basis for the rejection is therefore moot.

With respect to the issue of predicting whether a particular genetic mutation will affect drug responsiveness, Applicant’s claims are now limited to mutations that decrease MTHFR enzymatic activity and thermal stability. As detailed above, at Table 9, applicant discloses a statistical analysis showing that schizophrenic patients having an MTHFR C677T mutation are significantly more likely to respond to a neuroleptic therapy than other schizophrenic patients. As indicated in the Declaration of Dr. Rima Rozen, paragraph 5, based on Applicant’s results with drug responsiveness in patients carrying the heterozygous MTHFR C677T mutation, one skilled in the art would expect that patients carrying mutations that have similar effects on the biochemical characteristics of MTHFR would also share a similar responsiveness to a neuroleptic therapy.

As applied to the present claims, the final basis for the enablement rejection may be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 34-44 and 50-52 stand further rejected, under 35 U.S.C. § 112, second paragraph, as being indefinite for reciting that the “subject is determined to comprise at least two MTHFR mutations.” This rejection is based on the assertion that it is not clear whether the method includes a step of analyzing a nucleic acid for the presence of the two mutations. Claims 34, 50, and their dependent claims have been amended to recite that the nucleic acid is determined to comprise at least two MTHFR mutations. Applicant notes that independent claims 29 and 45, from which claims 34 and 50 depend, require the analysis of an MTHFR nucleic acid in a sample obtained from a subject. Subsequent to this analysis, as recited in claims 34 and 50, the presence of two mutations is determined. The claims clearly require the analysis of a nucleic acid prior to determining the presence of a mutation. This basis for the indefiniteness rejection may be withdrawn.

In addition, the Office asserts that it is unclear how the identification of additional MTHFR mutations affects the choice of therapy. This rejection is respectfully traversed.

As detailed above, as the number of mutations affecting MTHFR function increases, there can be a corresponding decrease in enzyme activity and thermostability and a resultant increase in plasma homocysteine level. Patients having increased levels of plasma homocysteine have an increased risk of exhibiting schizophrenic symptoms and an increased likelihood that those symptoms will be severe. Accordingly, such patients are

more likely to benefit from neuroleptic therapy than patients that are less ill. This basis for the indefiniteness rejection may also be withdrawn.

With respect to the indefiniteness rejection of claims 37-44, Applicant notes that these claims have been cancelled and this rejection is now moot.

Conclusion

Applicant respectfully submits that submit that this case is in condition for allowance, and such action is respectfully requested. If the Office does not concur, a telephonic interview with the undersigned is hereby requested.

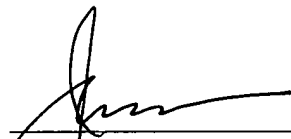
Enclosed is a Petition to extend the period for replying to the final Office action for one month, to and including March 19, 2004, and a check in payment of the required extension fee.

If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 19 March 2004

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